Error Rates Resulting From Anemia can be Corrected in Multiple Commonly Used Point-of-Care Glucometers

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Background: **A point-of-care (POC) glucometer (G1) used for critical care at our institution is inaccurate in the presence of low hematocrit (HCT) values. The purpose of this study was to analyze error rates of three additional POC glucometer brands and determine mathematical correction formulas for each.**

Methods: **Blood samples (n = 196) from a cohort of surgical, trauma, medical, cardiothoracic, and burn intensive care unit patients were tested on three commonly used POC glucometer brands (G2–G4). Results were compared with reference laboratory values, and correction compared with the validated formula for G1. A mathematical formula specific to each glucometer type was derived from glucose measurements, associated HCT values, and the degree of difference relative to laboratory results.**

Results: **POC glucometer results were consistently elevated compared with reference laboratory values. Glucometer error rates for HCT ≤ 25% ranged from 15.4% to 22.3% for the three types. Error rates for 25% < HCT < 34% ranged from 16.4% to 18.4%. A correction formula for each glucometer based on the natural log transformation of the HCT predicted reference values with a mean error rate of −0.54% ± 5.6% for G2, −0.6% ± 5.5% for G3, and 0.2% ± 8.0% for G4. Correction was similar to that previously established for G1 (−0.01% ± 4.8).**

Conclusions: **Significant error rates because of HCT effect were found in all glucometer models tested with accurate prediction of reference values with a simple mathematical formula.**

Key Words: **Glucometer error, Hypoglycemia, Hematocrit effect, Diagnostic accuracy.**

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Accurate glucose measurement is an essential requirement for tight glucose control in the critical care environment. Previous studies demonstrated, however, that outpatient point-of-care (POC) glucometers, the most common method used for bedside glucose measurement in burn intensive care units (ICUs) (Mann, unpublished data, USAISR), have unacceptable error rates because of low hematocrit (HCT) values.[1–13] Use of these devices in anemic patients results in erroneously high glucose measurements compared with laboratory reference values.

Implementation of tight glucose control occurred simultaneously with adoption of restrictive transfusion strategies, increasing the prevalence of both hypoglycemia and anemia in the ICU.[14–20] The change in allogeneic blood transfusion practices occurred in response to work by Hebert et al.[21,22] demonstrating that blood could be safely withheld until hemoglobin levels drop to 7 mg/dL or below, reducing transfusion-related risk. As physicians adopted practices that resulted in permissive anemia, the number of critically ill patients at risk of inappropriate insulin management from HCT error increased. POC glucose meters, commonly used in ICUs for bedside glucose measurement, overestimate blood glucose measurements in samples with low HCT levels.[4,5,7,8,12] The error occurs because decreased red blood cell causes less displacement of plasma, resulting in the presence of relatively more glucose molecules available to react with the enzyme; this is coupled with an assumed plasma volume that is smaller than actual. Glucometer error rates of 15% to 20% were considered acceptable before implementation of tight glycemic control; however, current narrow glycemic targets necessitate greater accuracy of measurement.

The association of glucometer error because of nonoptimal HCT levels is recognized.[1–13,23] Studies at this institution demonstrated that errors in a single-channel glucometer (G1) were systematic and reproducible, resulted in inappropriate therapy, and could be corrected with a simple mathematical formula. A survey conducted at this institution of all American Burn Association-verified burn centers (N = 44) found that POC glucose

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analyzers are used to manage intravenous insulin therapy at 95% of centers (42 of 44). Of these, four are common, including the previous single-channel glucometer (G1) studied (Mann, unpublished data, USAISR). Our hypothesis for the current study is that the three remaining POC glucometer brands (G2–G4) are subject to the same degree of systematic error when measuring blood glucose in low HCT samples. We further speculated that mathematical correction formulas can accurately predict laboratory glucose values within an error rate of 5%.

MATERIALS AND METHODS

Approval for our study was granted by the Brooke Army Medical Center Institutional Review Board. We conducted prospective collection of blood samples from critical care patients at a Level I trauma and burn center from December 2006 to February 2007. Samples were taken from all critically ill ICU patients with stable HCTs and central venous or arterial access in the trauma, surgical, combined medical and cardiothoracic, or burn ICU. Patients with unstable HCT levels as a result of active bleeding or transfusions were excluded to ensure validity of the glucose to HCT comparison. Three commonly used POC glucose analyzers were labeled G2 to G4 and tested against reference laboratory glucose measurement: Accu-Chek Inform (Roche Diagnostics, Indianapolis, IN), Accu-Chek Advantage (Roche Diagnostics, Indianapolis, IN), and Medisense Precision PCx (Abbott Diagnostics, Abbott Park, IL). The method of glucose analysis for each device is given in Table 1. Results from the three test glucometers were compared with reference laboratory serum analyzer values (Vitros Fusion, Ortho Clinical Diagnostics, Rochester, NY). Error rates for all models were compared with those previously established for the G1 model (SureStep Flexx, LifeScan, Milpitas, CA).

Quality control testing was conducted on each POC analyzer before every data collection period; all tests were performed by trained operators certified by quality control personnel on the use of POC devices tested in the study. Contamination of the sample to be measured was minimized by using arterial blood whenever possible. If arterial access was unavailable, central venous line infusions were halted and 10 mL of blood withdrawn into the in line aspiration chamber (SAFESET reservoir, Hospira, Lake Forest, IL) before sample collection. Capillary blood was not used. A 3-mL volume of blood was withdrawn and the blood was immediately applied to the meter strips per the manufacturer's guidelines. Two mL of blood from the same sample were sent to the laboratory in sodium fluoride gray-top evacuated collection tubes (BD, Franklin Lakes, NJ) for serum laboratory analysis.

Each blood sample was simultaneously tested by eight glucometers (two of each model) to reduce inherent intradevice variance. Glucose measurement was performed according to manufacturer recommendations and reagent testing strips for a given model were taken from the same lot. Glucometer operators were blinded to reference values, and laboratory technicians were blinded to glucometer measurements.

Mathematical correction formulas were developed to determine goodness of fit for each of the tested POC glucometers using MATLAB (The MathWorks, Natick, MA). Nonlinear component regression was performed because HCT has a nonlinear effect on accuracy of POC glucometers. A dual parameter correction factor was used to modify the linear correction formula with a nonlinear HCT value. Formulas were tested and compared for goodness of fit with respect to reference values.

A biasing set of values was included in the nonlinear regression models to assure proper correction of the formulas at extreme glucose and HCT values. Datasets for each POC device were analyzed for average error, a maximum and minimum HCT was calculated; the biasing set was then computed by generation of an expected model response of the POC device at the two HCT extremes for a set of extreme glucose measures. Correction formulas were considered valid if the mean error was $<1\%$ from the laboratory reference values. Calculation of error rates consisted of comparison of the device value against the serum reference value and reported using the formula: percent error rate = (glucometer value − reference value)/reference value × 100.

Validation for the three test device models was performed using a Monte Carlo[24] approach consisting of a randomly selected subset of glucose samples with calculation of the error rates of the chosen subset. The validation algorithm used a set of 1,000 iterations for error calculation with the 50% randomly selected subset. Final mean validation error and SD of the error was calculated to obtain an overall error value for each of the models. Corrected and uncorrected glucose measurements were plotted via the Bland-Altman method.[25]

All statistical analyses were performed using the SPSS (SPSS, Chicago, IL) or SAS (SAS Institute, Cary, NC) programs. Analysis was performed using Wilcoxon's signed ranks test for all comparisons.

Table 1 Profile of Tested POC Glucose Measuring Devices (HCT–Hematocrit)

Glucometer	Reported Range of Accuracy	Test Method	Enzyme	Specimen
G1 (SureStep Flexx)	HCT 25–60%	Photometric	Glucose oxidase	Whole blood
G2 (Accu-Chek Inform)	HCT 20–65% (<200 mg/dL)	Amperometric	Glucose dehydrogenase	Whole blood
G3 (Accu-Chek Advantage)	HCT 20–65% (<200 mg/dL)	Amperometric	Glucose dehydrogenase	Whole blood
G4 (Precision PCx)	HCT 20–70% (20–600 mg/dL)	Amperometric	Glucose oxidase	Whole blood

RESULTS

Samples were collected during 17 nonconsecutive days (n = 196) for use in formula development. Study related glucose samples were obtained within 12 hours of the daily complete blood count (CBC) measurement. Nine Accu-Chek Inform measurements could not be obtained because of battery failure on one test day. Arterial blood samples (n = 108) were used exclusively to develop the Precision PCx formula. Power was greater than 0.99 for all four glucometer data sets.

Samples were obtained from the trauma (n = 36), surgical (n = 46), medical and cardiothoracic (n = 58), and burn (n = 55) ICUs. Glucose values from all units ranged from 59 mg/dL to 299 mg/dL with a mean of 129 mg/dL (SD 35.6). Mean HCT per sample was 27.8% (SD 4.3%). As with the first glucometer studied (G1: Glucometer value × 0.2104 × LN(HCT × 3.3249) – 11.3934; LN = natural log) prediction formulas were developed for all three models, and are as follows:

$$\text{G2 Glucometer value} \times 0.8368 + 1.959 \times \text{LN(HCT)} - 3.621$$

$$\text{G3 Glucometer value} \times 0.8248 + 3.3895 \times \text{LN(HCT)} - 7.6008$$

$$\text{G4 Glucometer value} \times 0.1866 \times \text{LN(HCT} \times 3.729) - 2.8203$$

For all models, uncorrected glucometer measurements were significantly different from reference laboratory glucose values and improved to within ±5% with formula prediction (see Table 2). Average glucometer error stratified by HCT was less than ±5% after correction (see Table 3) demonstrating that accuracy was improved in all cases. Manufacturers of all three models tested claim that results are reliable to HCT levels of 20%, yet uncorrected error rates of all three glucometers were greater than 15% for HCTs less than 34%.

Correction was confirmed with model validation by the Monte Carlo method (Table 4) demonstrating that mean percent error of less than ±5% after correction was possible for all devices tested. Validation results were comparable to those previously achieved for G1 glucometer correction. Bland-Altman plots demonstrated a size effect[25] in uncorrected glucometer results for G2 and G3, but not G1 or G4 (see Figs. 1–4). No size effect was evident after correction, and average mean difference approximated zero in every case.

Table 4 Results of Model Validation for Each Glucometer Type

Glucometer	Mean Error ± SD (%)	Mean Standard Deviation ± SD (%)
G1 (n = 197)	0.44 ± 0.35	4.88 ± 0.30
G2 (n = 187)	–0.56 ± 0.40	5.58 ± 0.32
G3 (n = 196)	–0.61 ± 0.40	5.51 ± 0.32
G4 (n = 108)	0.24 ± 0.78	7.90 ± 0.86

Random subsets comprised of 50% of dataset were selected from all samples. Monte Carlo validation was performed 1,000 times and averaged to converge to mean error.

Table 2 Percent Error for Uncorrected and Corrected POC Glucometers and Difference From Reference Laboratory Value. Mathematical Correction Results in No Difference Detected Compared With Reference Laboratory Values

Glucometer	Uncorrected % Error Mean, SD % (Range; min to max %)	Uncorrected vs. Reference Mean *p* Value	Corrected % Error Mean, SD % (Range; min to max %)	Corrected vs. Reference Mean *p* Value
G1 (n = 196)	16.0, 7.5 (42; –6.07 to 36.2)	<0.0001	–0.01*, 4.8 (30; –14.5 to 15.5)	NS
G2 (n = 187)	16.0, 6.7 (41; –3.9 to 37.1)	<0.0001	–0.54*, 5.6 (35; –17.2 to 17.7)	NS
G3 (n = 196)	16.9, 6.7 (41; –5.4 to 35.9)	<0.0001	–0.6*, 5.5 (33; –18.9 to 14.5)	NS
G4 (n = 108)	18.7, 10.1 (70; –11.4 to 59.0)	<0.0001	0.2*, 8.0 (54; –21.3 to 33.0)	NS

* $p < 0.0001$, uncorrected versus corrected % mean error.

Table 3 Percent of Error by Hematocrit (HCT) Range for Each Glucometer Before and After Mathematical Correction

Glucometer	Uncorrected Error			Corrected Error		
	<25% HCT (SD %)	25%–34% HCT (SD %)	> 34% HCT (SD %)	< 25% HCT (SD %)	25%–34% HCT (SD %)	>34% HCT (SD %)
G1	20.6% (5.2), n = 49	15.2% (7.3), n = 132	7.5% (6.5), n = 15	–0.24%* (4.2), n = 49	0.78%* (5.0), n = 132	0.04%* (5.4), n = 15
G2	15.4% (6.7), n = 46	16.4% (6.6), n = 126	15.5% (7.8), n = 15	–1.6%* (5.5), n = 46	–0.5%* (6.9), n = 126	–0.5%* (6.9), n = 15
G3	17.1% (7.4), n = 49	17.0% (6.5), n = 132	15.5% (7.3), n = 15	–1.0%* (5.9), n = 49	–0.4%* (5.3), n = 132	–1.2%* (6.1), n = 15
G4	22.3% (8.0), n = 28	18.4% (10.3), n = 69	11.7% (10.3), n = 11	–1.12%* (6.6), n = 28	0.78%* (8.3), n = 69	–0.16%* (8.8), n = 11

The HCT level identified for G1 for significant error is 34% (% error = glucometer value - reference value/reference value × 100).
* $p < 0.0001$ uncorrected versus corrected % mean error.

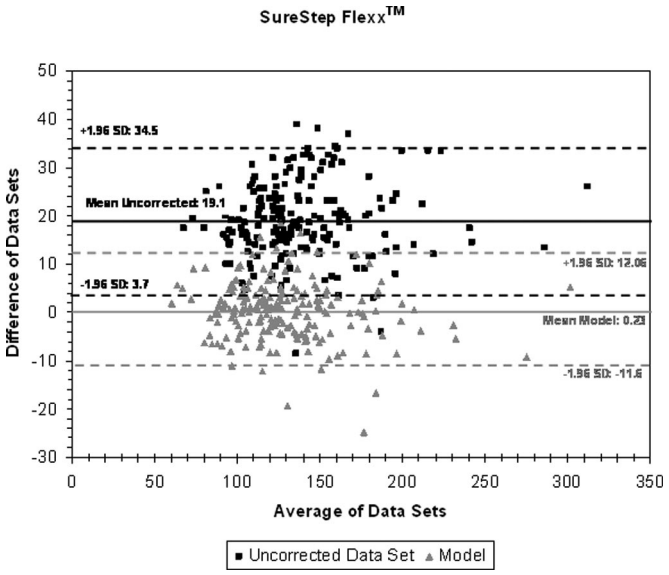

Fig. 1. *Bland-Altman graph of differences between measured glucometer values and mathematically corrected values for the SureStep Flexx (LifeScan) glucometer model.*

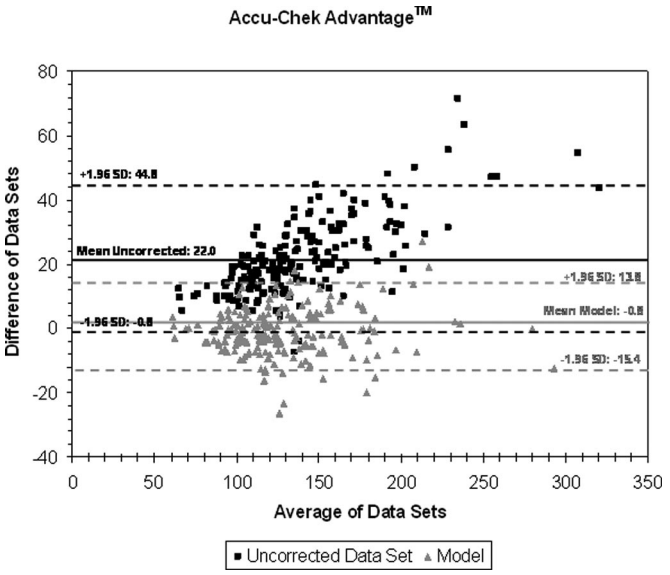

Fig. 3. *Bland-Altman graph of differences between measured glucometer values and mathematically corrected values for the Accu-Chek Advantage (Roche Diagnostics) glucometer model.*

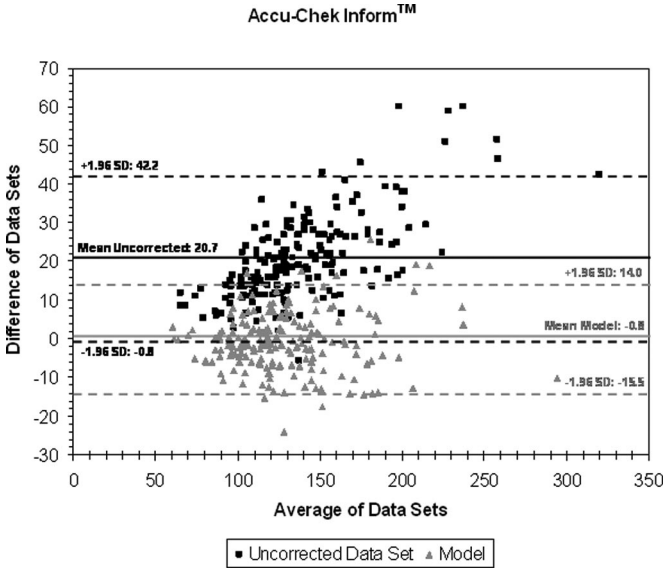

Fig. 2. *Bland-Altman graph of differences between measured glucometer values and mathematically corrected values for the Accu-Chek Inform (Roche Diagnostics) glucometer model.*

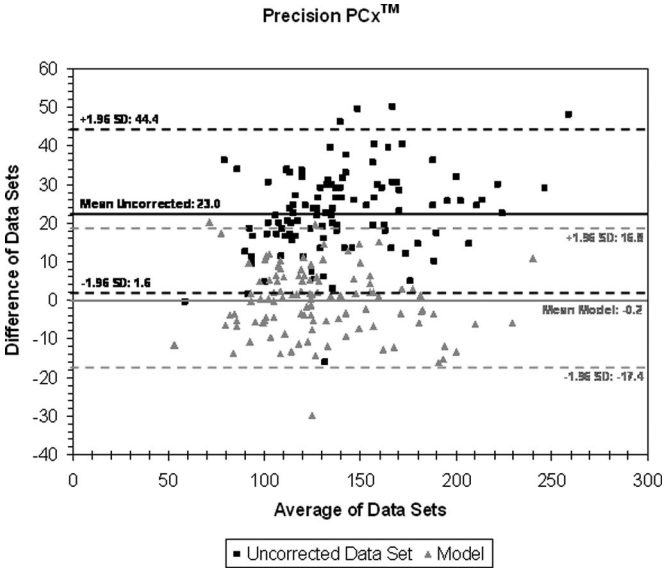

Fig. 4. *Bland-Altman graph of differences between measured glucometer values and mathematically corrected values for the Precision PCx (Abbott Diagnostics) glucometer model.*

DISCUSSION

The findings published by Hebert et al.[21] resulted in significant changes in management of transfusions in critically ill patients.[14–19,26–28] Van den Berghe et al.[29] subsequently demonstrated mortality and morbidity benefits associated with intensive insulin therapy, leading many critical care specialists to lower target glucose values for their patients.[29–36] These two studies simultaneously increased the prevalence of hypoglycemia and anemia in critical care patients, resulting in unanticipated inaccuracy of POC glucose analyzers.

Tight glucose control mandates frequent blood monitoring, and "turn-around" times for laboratory analysis are too cumbersome for safe use in the ICU. POC glucometers are the standard of care in bedside glucose management in most ICUs, yet clinicians are largely unaware that manufacturers consider error rates of 15% to 20% to be acceptable. This stems from outdated Food and Drug Administration (FDA) standards developed when maintenance of blood glucose levels less than 200 mg/dL was the standard of care. These devices, developed for the diabetic outpatient, do not meet accuracy expectations for management of the critically ill

patient receiving intensive insulin therapy. The FDA standards for POC glucose analyzer accuracy recommend that average error be no more than 15% of reference values,[24] however the American Diabetic Association 1996 consensus statement[37] suggest the error in glycemic measurement should be no more than 5%. Manufacturers do not even adhere to the FDA guidelines; product literature describes accuracy of only 20% of the reference value.[38]

We previously confirmed that low HCT effect causes systematic glucose measurement error in a single-channel glucometer, resulting in routine overestimation of blood glucose by 20% or more when compared with the reference laboratory value (Pidcoke, unpublished data, USAISR). In addition, we demonstrated that a correction formula was able to predict reference laboratory glucose levels with an error rate of less than 5%. Before correction the glucometer underestimated glucose values of less than 80 mg/dL by 80%. For example, a patient with a HCT of 25% and a glucometer reading of 80 mg/dL should have an actual glucose level of 62 mg/dL, and without correction it would not be recognized in time to provide appropriate therapy. Similarly, an uncorrected glucometer will over report values above 110 mg/dL 50% of the time, resulting in excessive insulin administration.

Our data demonstrate that mathematical correction of POC glucose analyzers to clinically acceptable error is possible. The correction formula for glucometer G1 has been used in our burn ICU since July 2006. To date no adverse events have been associated with use of the formula and data comparing time periods before and after implementation reveal a 50% reduction of hypoglycemic values in the burn ICU (Pidcoke, unpublished data, USAISR).

We identified the inflection point for clinically significant HCT effect for G1 occurs at HCT of 34% using a large database comprised of approximately 13,000 matched data points of glucometer readings and laboratory values with associated HCT levels (Pidcoke, unpublished data, USAISR). HCT measurement of 34% is not a degree of anemia most providers would consider to be clinically relevant, yet this is the point where the reliability of this glucometer deviates from the 95% confidence interval of clinically acceptable error. Values much lower would be expected in the practice of providers adopting the restrictive transfusion practices proposed by Hebert et al.[21,22]

In the present study, we provide evidence that the previously reported error is present in multiple models of commonly used glucometers. Other investigators have reported better glucometer performance in models using the enzyme glucose dehydrogenase, yet we found error rates to be comparable for all four brands, regardless of the enzyme reaction used for measurement. The meters tested in our study demonstrate consistent error well over this acceptable range, yet when corrected with the derived formula incorporating HCT, we achieved excellent correlation with reference values and error less than 5% for all tested meters.

This study is limited to a single center with small sample sizes from the variety of intensive care settings and limited ranges of HCT and glucose levels. Identification of the inflection point for clinically significant error by the device was performed on data measured with one glucometer brand only. The study was executed by experienced operators who performed all measurements to ensure scientific reliability; however, greater variability in measurement may occur in actual clinical practice. Glucometer glucose measurement was paired to the most recent HCT value, and thus patients with unstable HCTs were excluded which may introduce bias.

Error as a result of low HCT is systematic and results from glucometer miscalculation of plasma displacement in whole blood samples and mathematical correction is possible. The correction formulas described in this study require further validation; however, they reverse the underreporting of low glucose values and therefore increase patient safety.

CONCLUSION

We confirmed that systematic error as a result of low HCT is found in multiple commonly used POC glucometers similar to that previously shown in a single channel glucometer. Error was amenable to mathematical correction in all models tested and reduced error rates to within 5% as recommended by the American Diabetes Association. Providers should assume glucometer error because of anemia is present at their institution until proven otherwise.

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DISCUSSION

Dr. Rajan Gupta (Lebanon, New Hampshire): The concept of tight glycemic control in ICU patients has been a topic of extensive debate for the last several years.

Since the publication of the Vanderberg study published in the *New England Journal of Medicine* in 2001, several reports have produced inconsistent results from the application of tight glycemic control.

It appears that certain patient populations may benefit in regards to in-hospital morbidity; however, it remains unclear if the same outcomes are true for all patients. Additionally, reduction in mortality has not been consistently demonstrated.

The authors of this study suggest that in this context of tight glycemic control, combined with restrictive transfusion practices, point-of-care glucose monitoring is inaccurate in our anemic ICU patients and that in this context the margin of error is reduced and previously accepted error rates as high as 20% are no longer acceptable.

In a different forum, the authors presented their data for a single point-of-care glucometer used in their ICU. They demonstrated that the bedside device consistently gave falsely elevated glucose readings in anemic patients and subsequently proposed a mathematical formula to correct for the false elevations.

In this study Major Mann and colleagues have extended their analysis to include three additional commonly-used glucometers. Once again they have proposed mathematical formulas specific to each device to correct for the falsely elevated readings.

The additional devices they studied are theoretically more reliable in that they use glucose dehydrogenase enzymatic reactions instead of glucose oxidase and that they employed amperometric rather than photometric detection technology.

However, it appears that despite these improvements all the devices remain inaccurate in the setting of anemia. I would like to commend Ms. Mann and the other authors for their work. It is timely and clinically-relevant for certain patient populations that might benefit from tight glycemic control.

Overall the study is well designed, the statistical analysis is appropriate and the results are valid. However, a few relevant questions deserve some consideration.

The first question extends from my review of the manuscript; however, one slide in the presentation may have partially addressed it, please clarify; did you eliminate patient-related confounding variables that may falsely elevate glucometer readings such as the level of oxygenation, especially in arterial samples being tested on devices utilizing glucose oxidase?

Number 2, did you account for source-related confounding variables? And, more specifically, did you note any difference in error rates between samples taken from arterial lines versus central venous lines? Did you identify any differences in error rates in the different patient populations you studied?

Number 3, why did you use hematocrit from the morning laboratory values and not measure hematocrit on the same samples that you measured the glucose levels?

Number 4, although you have successfully demonstrated a significant reduction in error rates with the application of the correction formulas as well as fewer hypoglycemic events by laboratory values, were there any demonstrable clinical values such as reduced number of hypoglycemic related mental status changes or lower infection rates?

Were you able to demonstrate any outcome differences such as less ventilator days or reduced ICU length of stay? In other words, does reducing the error rate from 20% to less than 5% really increase patient safety?

Finally, more of a consideration than a question, rather than develop mathematical correctional formulas every time a new device is introduced into the market, other authors have suggested perhaps the target range proposed by Vanderberg and others simple needs to be adjusted for anemic patients.

Maj Elizabeth A. Mann (San Antonio, Texas): I would like to say that as far as confounding variables, there is a new four-channel glucometer available on the market. We did prospectively test it on 100 samples. That data will be presented at the February 2008 SCCM Congress but, bottom line, we found statistical equivalency between the four-channel glucometer that does reduce all eliminating variables and our correction factor adjusting for hematocrit alone.

We used the morning hematocrit from the lab, 1) to reduce phlebotomy from our patients and, 2) for logistical reason with our coordination with the lab for this large study. It is a limitation. In future studies we will plan to take concurrent blood sample for CBC as well as the laboratory glucose as well as replicate the laboratory glucose at least twice.

Central line versus arterial line samples, that will be available in the paper; however, from just a cursory review there appears to be no statistical difference from those two different sample sources.

You asked about demonstrable clinical differences. This was not a study designed or powered to look at outcomes.

I think from a review of the literature and work that we're doing with computer decision support insulin titration, time in glucose range seems to be the critical factor in eliminating infection and other morbidity in patients; but we will be looking at that in the future. Because we use the correction factor in our ICU, that can be part of the upcoming study.

And finally, your comment about adjusting our titration range rather than having an absolute value to treat, unfortunately that's logistically difficult because many centers use laboratory glucose, some use ABG machines, some use hemocue machines. It would be impossible to simply change the range because all these methodologies measure glucose differently.

We believe it is better to have reliable measurements to ensure that you know what your glucose is when you measure it and this cheap, basically free mathematical correction is a mechanism to do so.